



# Cardio-oncology discipline: focus on the necessities in developing countries

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## Abstract

Cardiovascular diseases constitute one of the main aetiologies of mortality among patients with cancer. Population ageing and cancer survival rate improvements have resulted in the coexistence of cardiovascular diseases and malignancies in an increasing number of patients. With the diversity in treatments and the introduction of new drug lines, multiple mechanisms of cardiovascular injury have been recognized in these patients.

Cardio-oncology is an emerging entity introduced to provide a proper solution to the several challenges encountered in the management of patients with cancer and cardiac involvement.

This review will assess the logical grounds for establishing a cardio-oncology unit, describe the main objectives and the detailed responsibilities in such systems, and outline the target population. Furthermore, the importance of research and appropriate data collection will be highlighted. Lastly, the special considerations and modifications required for setting up such centres in the developing countries are discussed.

**Keywords** Cardio-oncology; Developing countries

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## Introduction

### Cardio-oncology: a noteworthy emerging discipline

Cancer and cardiovascular diseases (CVDs) are the two most common non-communicable diseases that cause the highest global mortality.<sup>1</sup> In recent years, the growing volume of elderly populations and the improvement in overall survival rates have led to the coexistence of CVDs and malignancies in a large group of patients.

Similarities have been observed among the patterns of the geographic distributions of the mortality of patients with CVDs and cancer, which are believed to be a result of common risk factors in the pathogenesis of diseases such as smoking, hyperlipidaemia, and obesity.<sup>2</sup> Additionally, there is an increased risk of CVDs and its risk factors among

candidates for oncological treatments.<sup>3</sup> On the other hand, the overall improvement in the treatment outcomes of patients with cancer has led to an increased incidence of the cardiovascular side effects of the mentioned treatments. Moreover, cardiovascular events have been recognized as a major cause of mortality among cancer survivors, which in some cancer types might exceed the mortality rate related to the reoccurrence of the baseline malignancy.<sup>4,5</sup>

With the increased survival of patients and the diversity in treatments, multiple mechanisms of injury have been recognized that can affect the entire cardiovascular system. Although there are no official guidelines, there exist recommendations regarding the monitoring and management of complications in different categories.<sup>6,7</sup>

Addressing the challenges associated with the care of these patients has ushered in a new branch of medicine called 'cardio-oncology'. The main purpose of this specialty

is to consider both aspects of cardiology and oncology in a patient, creating a bridge between the two fields in order to make the best decisions regarding the prevention, monitoring, and treatment of the diseases. An overview of the general design of a cardio-oncology unit (COU) is depicted in Figure 1.

In this review article, we aim to describe the rationale for establishing a COU. Furthermore, we will explain the general objectives and the detailed responsibilities in such systems, identify the target population, and define the importance of research in this context. Lastly, we will discuss the special considerations and modifications required for establishing such centres in developing countries.

## Purpose

Cardio-oncology services are designed to provide extensive cardiovascular care to patients with cancer. This comprehensive care includes actions before, during, and after the completion of the cancer treatment (Figure 2).

A complete evaluation of the patient's baseline cardiovascular state, risk factors, and previous history should be performed prior to the initiation of any treatment. Subsequently, risk stratification is done based on the mentioned assessments. Primary prevention measures should be implemented as needed, and the treatment of any underlying cardiovascular conditions should be optimized. The cardiovascular risk of each treatment strategy should be discussed

carefully within the cardio-oncology team and weighed against its effectiveness in cancer treatment. Finally, when the proper treatment is selected, the means and frequency of monitoring the cardiovascular function during the treatment process should be planned. Importantly, lack of specific cardio-oncology discipline might result in the misclassification of patients into higher cardiovascular risk categories and, consequently, their deprivation of a vital chemotherapy programme.

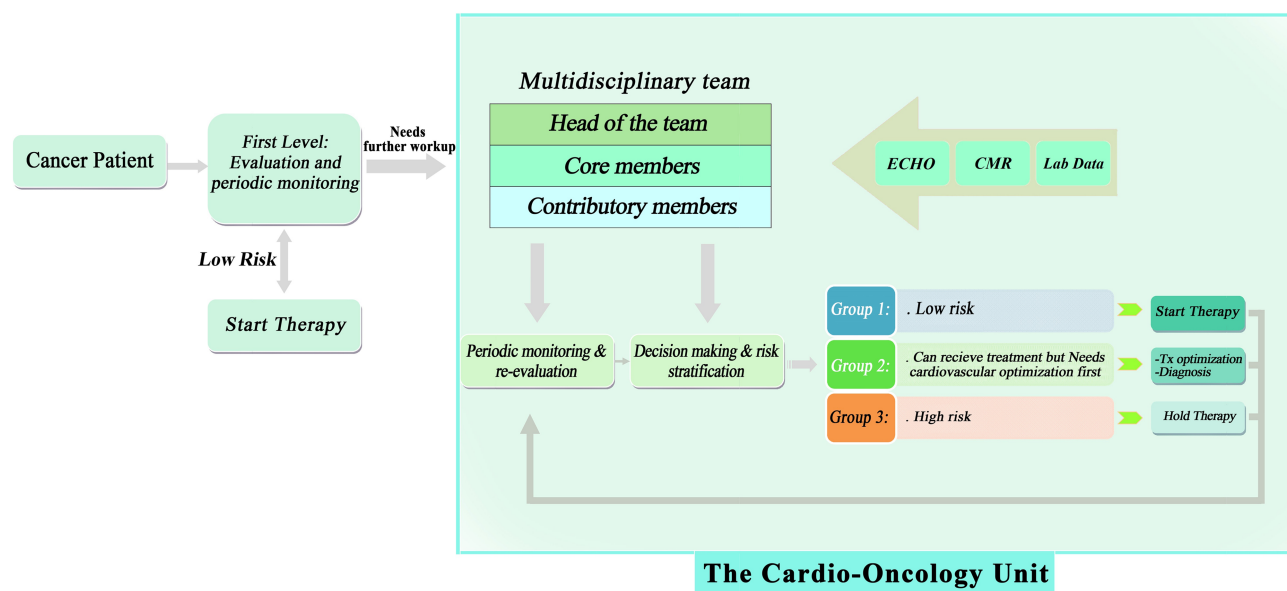
During the course of treatment, ongoing and arranged monitoring should be implemented. When cardiovascular side effects are encountered, the challenging decision will be to determine whether to continue or discontinue the treatment. The goal is to interrupt the cancer treatment as briefly as possible while minimizing the detrimental effects on the cardiovascular system. Of note, one study linked the interruptions in trastuzumab courses with a higher rate of cancer recurrence among patients suffering from breast cancer.<sup>6,8,9</sup>

Long-term side effects of cancer treatments can develop years later. Therefore, the selection of the proper strategy for long-term follow-ups after the completion of treatment and the adherence of patients to the programme are important.

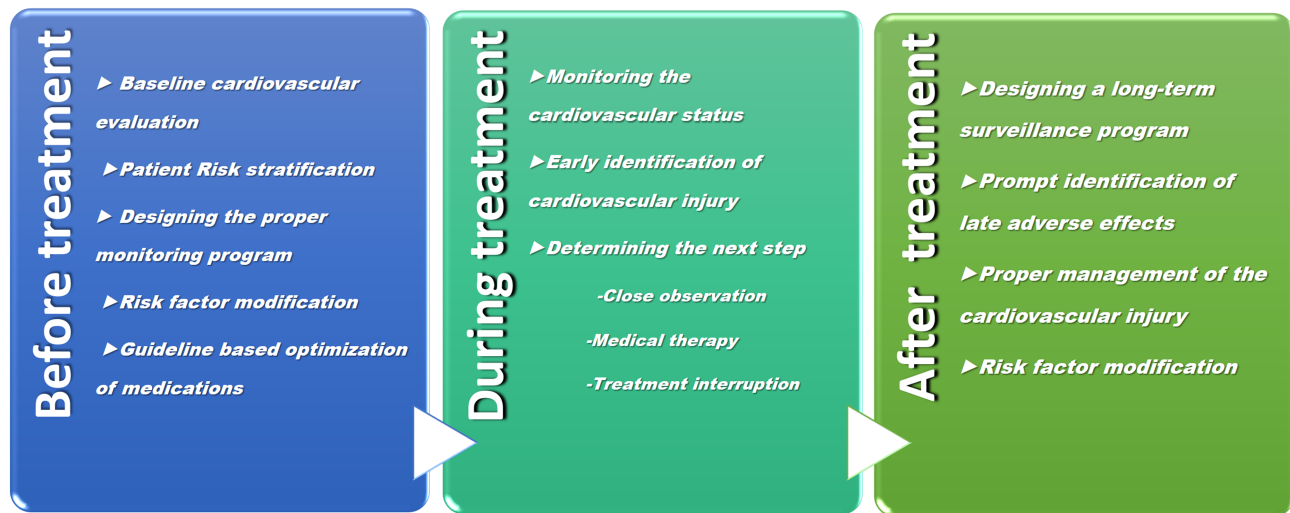
Although the main focus of cardio-oncology has been the monitoring and treatment of the cardiovascular toxicity of cancer therapies, several other issues need to be addressed in this regard.

Evidence shows that cardiac surgeries have an increased rate of complications and mortality among patients suffering

**Figure 1** Overview of the design and function of a cardio-oncology unit. After first-level evaluations, patients in need of further workup are referred to the cardio-oncology unit, where risk stratification based on imaging and laboratory data is performed and individualized treatments and monitoring programs of each patient are planned. CMR, cardiac magnetic resonance imaging; LAB, laboratory.



**Figure 2** Objectives of the COU during the stages of cancer management. Detailed objectives of a COU, before, during, and after cancer treatment are illustrated. COU, cardio-oncology unit.



from cancer with a history of radiation. This includes both patients with radiation-induced valvular disease that require surgery (increased operative mortality of 3.8% vs. 0.8% and a 2.2-fold higher risk of decreased long-term survival)<sup>10</sup> and patients with a history of radiation that need cardiac surgery due to other aetiologies such as coronary artery bypass graft surgery (72% survival rate after  $7.6 \pm 3$  years follow-up in the control group vs. 45% survival in the radiation group).<sup>11</sup> Considering the mentioned complications in surgical procedures, interventional strategies such as transcatheter aortic valve implantation and percutaneous coronary intervention are performed increasingly among these patients.<sup>12</sup> Indubitably, the application of interventional strategies in this high-risk population needs meticulous risk stratification.

A significantly increased rate of acute coronary syndromes (up to threefold) has been reported among patients with cancer, especially those with active malignancy.<sup>13</sup> The hypercoagulable state, increased bleeding risks, and the probable need for withholding antiplatelet agents are some of the main challenges encountered in choosing the optimal management strategy.<sup>14,15</sup>

## Logistics and requirements

### Team members and staff

A number of specialists and healthcare providers are prerequisites for a successful COU. A cardio-oncologist, a cardiologist with some expertise in heart failure or cardiac imaging, is often considered to be the leader of the team.<sup>16,17</sup> Medical

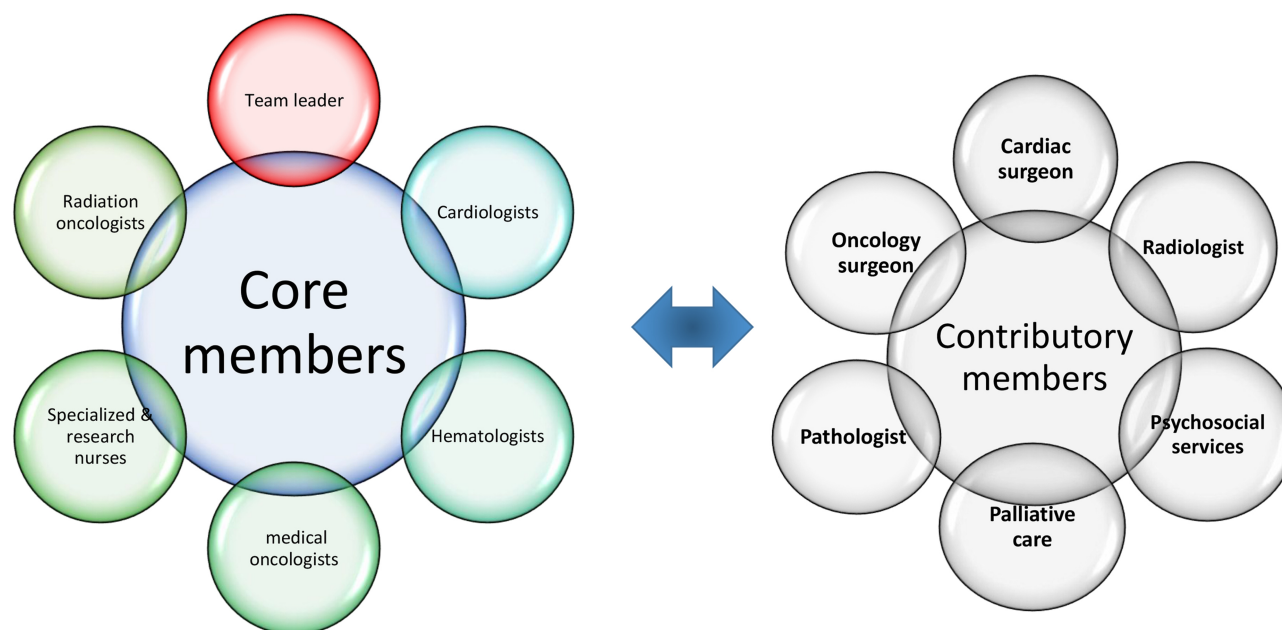
oncologists, radiation oncologists, and haematologists are the other members that comprise the core of the team, along with nurses that specialize in the field. Other healthcare professionals including surgeons, pathologists, palliative care specialists, nutritionists, and psychologists may assist the team on a case-based basis (Figure 3).<sup>6,7</sup> Furthermore, primary care physicians are regarded as the supportive members of cardio-oncology teams on the strength of their contribution to the risk-factor modification and long-term surveillance of patients.

### Location

The COU can be set up in an oncology centre or a cardiology-based establishment. A clear consensus has yet to emerge on what constitutes the most appropriate approach, and there are several pros and cons to each of the choices.

A clinic set-up in an oncology-based hospital confers better accessibility to patients. The rate of loss to follow-up can also be diminished by allowing patients to receive both cardiology and oncology visits at the same location and preferably in the same session. Furthermore, this approach can facilitate the communication between the cardiologist and the oncologist and provide more desirable contributions to tumour boards and oncology grand rounds. On the other hand, accessibility to cardiovascular imaging modalities may be limited within the oncology-based clinic, and the staff will also be less familiar with the routine measures of cardiovascular care or information to provide to patients, which favours the cardiology-based setting.

**Figure 3** Cardio-oncology team members. Team members consist of two groups: core members including the team leader, who should be invariably engaged in each patient's management process; and contributory members from various specialties, who are consulted on a case-based basis and as needed.



## Workflow

As awareness regarding the need for the COU is raised, institutional structures, protocols, and resources can be arranged.

Promoting and publicizing the cardio-oncology centre and its mission are of great significance. Presentations, workshops, letters, and face-to-face conversations should be used in order to increase awareness regarding the importance of this relatively novel entity and the need for its development among various levels of healthcare professionals.<sup>18</sup>

The clinical model of the unit should be designed thoroughly. There is a wide spectrum of cardiovascular adverse effects due to cancer treatment. Considering the limitations in resources and services, especially in the initial stages of establishing these centres, it is vital to define and limit the exact services that will be covered by the unit before initiating the process. Detailed descriptions of which patients are to be referred to the clinic must be defined. The volume of the work should be predicted and planned to be fully manageable by the available resources. For instance, a COU in a referral centre for patients with breast cancer should be experienced about cardiotoxicity management and equipped with selected imaging modalities recommended for a precise evaluation of the left ventricular systolic function. Nonetheless, in a centre with the target population of gastrointestinal malignancies, the focus of evaluations should be on monitoring blood pressure and QT prolongation, which are the main side

effects of vascular endothelial growth factor receptor inhibitors.<sup>19</sup>

Another issue that should be considered is the ease of communication between the cardiology and the oncology teams and their access to patients' medical records. Changes in treatment or imaging results and lab data should be well documented and readily accessible to all team members. In this regard, electronic documentation is the preferred method as it simplifies data sharing among different departments; still, in the case of unavailability, classic methods can also be implemented.<sup>20</sup>

It has been demonstrated that increased waiting times for chemotherapy can result in decreased survival among patients with cancer.<sup>21–23</sup> The optimal goal of the team is to deliver the required services on a same-day basis. This may not be feasible depending on the availability of resources in some units, but solutions and practical approaches to reach this goal should be sought. In the event of persistent shortages of resources, patients can be prioritized at the discretion of the team's oncologist. Electronic consultations have been arranged in some centres to facilitate and expedite the process and to reduce the need for the transportation of patients between centres. However, some studies have shown that patients favour face-to-face consultations.<sup>19</sup>

The multidisciplinary approach of the team should be implemented as was discussed earlier. The cardiologist in charge of patients should be in close and continuous communication

with the oncologists, and they should plan the treatment programme together considering the cardiovascular and oncological aspects of the disease. Any changes during the planning of the treatment or after the initiation of the treatment course should be addressed in the same manner.

Finally, patients' contribution and adherence to the programme are crucial. It is the responsibility of the team members, not least the professional nurses, to inform patients about the importance of continuous cardiovascular monitoring while undergoing cancer treatment. The common cardiovascular symptoms of treatments should be explained to patients and their caregivers so that they are alert in case side effects occur. Furthermore, accurate schedules and frequent reminders should be provided by the medical staff to patients, especially in the post-treatment stage when late cardiovascular side effects may develop.

## Education and training

With the increasing rate of cancer survivors and their common comorbidities, a more significant shortage of staff and professionals in the field is predicted in the near future, which highlights the need for the training of expert healthcare providers in this regard.

A comprehensive understanding of diagnostic and therapeutic methods in oncology and cardiovascular medicine will result in the optimal management of patients suffering from cancer with a concomitant focus on the cardiac and oncological aspects of the disease, which could eventually lead to better outcomes. The aim of cardio-oncology fellowship training programs is to achieve such insights.<sup>24</sup>

Research has shown that cardio-oncology lectures were included in only 10% of cardiology training curricula, and 40% of cardiology programs did not have any official training course for oncology-related topics.<sup>25</sup>

Training programs for cardio-oncology are defined at three levels by the International Cardio-Oncology Society and the Canadian Cardiac Oncology Network.<sup>24</sup> Level 3 is considered a fellowship and consists of at least a 1-year training programme in this field. The trainee is usually a cardiologist but could also be an oncologist.<sup>24,25</sup> Level 2 education is mostly for primary care providers and includes the awareness of potential CVDs and insights regarding the optimal time to refer a patient to a specialist. Level 1 education encompasses a basic understanding of issues concerning the cardio-oncology subject.

Strong fellowship programs require high-volume centres with in-patient and out-patient clinics. Faculty members with expertise in advanced imaging modalities such as echocardiography, magnetic resonance imaging, and nuclear medicine are essential. Ideally, heart failure specialists, electrophysiologists, interventionalists, and also cardiac surgeons should be accessible for consultations.<sup>25</sup>

## Research

Research is the cornerstone of a COU. As cardio-oncology is a newly recognized concept, the evidence regarding this field is limited. There are no official guidelines in the cardiovascular management of oncology patients, with only a few recommendations having been made in this regard.<sup>6,7,9</sup> Establishing an organized COU can expand our understanding of the related issues, help develop new evidence, and gather reliable data.

Each patient in the COU has different categories of medical data (demographics, imaging, and pharmacology). Therefore, strong multilayered databases are needed. Designing clinical registries leads to accurate and goal-oriented data collection and is a necessity for improvement in research quality.

Conducting clinical trials and participating in multicentre studies result in an increased knowledge in the field. Implementing the mentioned activities will eventually lead to practical guidelines and recommendations in this field.

## Cost effectiveness

Although there is increasing enthusiasm regarding the multidisciplinary management of patients, evidence on the true value of this approach and its cost effectiveness is still lacking. There has yet to be a study evaluating the cost effectiveness in the specific cardio-oncology multidisciplinary setting. Nonetheless, studies on the multidisciplinary management of patients with cancer have had variable results.<sup>26</sup> Previous research has shown that the multidisciplinary management of patients with cancer has conferred a more optimal staging assessment and improved adherence to the guidelines.<sup>27</sup> A recent study showed improved survival in patients with haematological and lung cancers that were assessed in multidisciplinary meetings. However, such benefits were not significant among patients with colorectal and breast cancers.<sup>28</sup>

Hence, further evidence is required to answer the question of whether or not these clinics are truly cost effective.

## Limitations and challenges

Some of the most common challenges in the implementation of COUs are summarized in *Table 1*.<sup>9</sup>

## Current status of cancers in developing countries

There is an undeniable link between the status of cancer prevalence and the need for COUs. Different facilities are



**Table 1** Challenges in implementing cardio-oncology unit

Lack of medical community awareness regarding purpose and function of the unit
Lack of specific guidelines and standardized administrative protocols
Lack of assigned infrastructure and financial support for the unit
Shortage of cardio-oncology units and Incompatible volume of patients to the available unit's capacity
Shortage of cardio-oncology experts

required based on different epidemiological statuses. It has been postulated that developed countries have reached a peak in the prevalence of cancers, which is expected to decrease in the upcoming years. However, currently, nearly two thirds of all cancer mortalities occur in low-income and middle-income countries.<sup>29</sup> Furthermore, a significant increase in the incidence and prevalence of malignancies is expected in the next few decades among developing countries. A study on cancer statistics in Iran predicted that there would be a twofold increase in cancer incidence among Iranians in the year 2035, compared with the year 2012, resulting in 184 481 new cases.<sup>30</sup>

General patterns in the prevalence and incidence of cancers are not similar among different countries, and there is diversity in different regions within the same country. The recognition of these patterns can be useful in terms of planning future programs and creating the required infrastructure for policymakers and healthcare providers in the field of cancer.

Based on a systematic analysis for the global burden of disease study by Fitzmaurice *et al.*, the most incident cancer among high-income countries was non-melanoma skin cancer, followed by prostate, colon and rectal, and lung cancers. Based on the same study, lung and breast cancers were the most incident cancers in middle-income countries, whereas cervical cancer still had the highest incidence among malignancies in low-income countries. The most incident cancers among Iran's population are reported to be breast, stomach, and prostate cancers, while stomach and lung cancers and leukaemia cause the highest mortality.<sup>31</sup> The most prominent increase in the country is expected to be among oesophageal, stomach, and prostate cancers in the upcoming years.<sup>30</sup>

The regional clustering of the prevalence of different cancers is another issue worth mentioning. Iran has witnessed an increase in the prevalence of breast cancer in its central (Tehran and Alborz) provinces as reported by a study conducted by Ahmadi *et al.*<sup>32</sup> The highest incidence of lung cancer is reported in central and also southern provinces,<sup>33</sup> while gastrointestinal cancers (especially oesophageal and stomach cancers) are more prevalent in the northern and north-western provinces of the country.<sup>34</sup>

The burst of cardiovascular risk factors and also malignancy-related predictors observed in developing countries is another issue of significance. A number of causes

contribute to this increase, the most prominent of which is the so-called 'westernization'. This phenomenon has many aspects including adopting a more sedentary lifestyle, dietary changes towards the use of more processed foods, higher intakes of meats and sweets, and behavioural changes. As an example, behavioural changes among women in low-income countries such as delayed childbearing, lower parity, and decreased rates of breastfeeding have caused trends towards an increased prevalence rate of breast cancer.<sup>30</sup>

The same challenges exist for the current increase in environmental and occupational exposures to carcinogens in the developing world. Lack of effective industrial hygiene, ineffective regulations, and inadequate education are the measures contributing to this increase.<sup>31</sup>

Apart from the important impact of environmental and occupational factors, the diversity of genetic background exerts a significant influence on the variability of cancer incidence.<sup>35</sup>

## Ongoing challenges

The main concern of the medical community involved in cardio-oncology is providing optimal services in terms of the early and effective identification and management of cardiovascular complications among patients with cancer. Devising preventive strategies to reduce the incidence of the mentioned adverse events would be a priority in this regard.

There are considerable variations in diagnostic and therapeutic processes in developing countries by comparison with the developed world. Studies have shown that more than 70% of breast cancer cases are diagnosed in the early stages (these numbers are above 90% in Norway and Sweden) in high-income countries. However, the percentages are significantly lower among low-income countries, and between 30% and 80% of patients are diagnosed in the advanced stages of III and IV, resulting in a remarkably increased burden of the disease.<sup>36</sup> This advanced group of patients is at a potentially higher risk of cardiac involvement due to both increased comorbidities and the need for more potent cancer therapies.

Different health policies and infrastructure are applied in developing countries based on the available resources. Cancer-screening programs represent an integral component of these policies in that they can lead to the earlier detection and survival improvement of patients. However, limited resources and financial problems in this part of the world require individualized approaches. Breast cancer screening is one of the most studied subjects in this regard. Research shows that implementing cost-effective screening programs such as down-staging with the purpose of raising awareness among patients and first-level health professionals and augmenting referral systems in lieu of such costly methods as mammography screening may be useful in the context of developing countries.<sup>36</sup>

The same strategy should be adopted in regard to cardio-oncology programs. Monitoring and follow-up methods should be modified based on the available infrastructure in the region. By way of example, recommendations concerning the monitoring of patients receiving anthracyclines suggest frequent measurements of the left ventricular global longitudinal strain. Still, this might not be practical considering that the required equipment is usually only available in tertiary centres in most developing countries. It is the art of the head of the cardio-oncology team to properly modify such recommendations without compromising the patient's care. In the mentioned scenario, the serial monitoring of cardiac biomarkers and Doppler evaluations of peak systolic mitral excursion are alternative practical and relatively inexpensive methods than can be primarily performed to identify high-risk patients and refer them to centres with the necessary tools for further evaluations.<sup>7</sup>

Significant strides have been taken in the therapeutic management of cancers and have improved the overall survival of patients in recent years. However, there are still multiple impediments to the treatment of patients with cancer in the developing world, influencing the related facilities such as cardio-oncology. Although there is a rather developed medical referral system in some developing countries, there is still room for improvement. Patients in need of multidisciplinary care are usually referred to a number of different medical centres for each of their consultations, sometimes even in different cities, which can be exhausting, especially for patients with cancer. Therefore, gathering the mentioned specialties in a COU not only can be convenient for the patients but also might be more cost effective.

While more than 60% of patients receive treatment in less than 3-month intervals after symptom onset in high-income countries, treatment is started in fewer than 30% of patients with breast cancer in a 3-month interval in low-income countries. This delay results from both an increased 'patient interval', defined as the time from symptom onset to seeking medical consultation, and 'treatment interval', which reflects the time from diagnosis until treatment commencement.<sup>36</sup>

The increasing costs of the emerging drug classes introduced to the market make them unavailable to a significant portion of patients in developing countries. Using generic drugs, increasing participation in global clinical trials, and expanding the insurance coverage are some of the policies that can be considered to overcome this problem.<sup>29</sup> Fortunately, apropos of cardiovascular therapeutic options for treating cancer-related complications, the required medications are mostly inexpensive, covered by insurance, and readily available. Consequently, an appropriate and organized system with effective screening for the early detection of cancer patients with cardiac involvement can provide the required therapeutic services.

Radiotherapy and its related cardiovascular complications are other topics of concern in cardio-oncology. Importantly,

the absence of widespread access to radiotherapy is an important issue in developing countries. It has been reported that about 50% of patients with cancer will need radiotherapy at least once during their illness. In low-to-medium-income countries, a higher percentage of patients are in need of radiotherapy compared with high-income countries.<sup>37</sup> This is in part due to the type of cancers. Additionally, as the tumours are recognized at higher stages, they are less amenable to surgery.

Zubizaretta *et al.* reported that 4221 teletherapy machines were available in low-to-middle-income countries, representing only 38% to 49% of the required devices based on the used benchmark. Of note, 39 of the countries did not provide any radiotherapy services. The same study suggested that between 4320 and 6958 additional machines were needed in these countries in order to meet patient demands.<sup>37</sup>

Finally, the growing number of patients undergoing cancer treatments warrants an expansion of cardiovascular monitoring systems. There are inconclusive data regarding the magnitude of patients currently covered by cardio-oncology programmes in developing countries. The equipment and expertise in each COU should be designated based on the specifications of the patients referred to the facility (e.g. the prevalent malignancies and their related treatment strategies in the region). Be that as it may, the majority of the few specialized facilities in this field are concentrated in large tertiary hospitals in central cities, limiting the nationwide access of patients.

## Research and education

Several issues appear to have been overlooked in developing countries. Data regarding the exact burden of malignancies are lacking, and most of the preventive, diagnostic, and therapeutic policies are based on the data and studies performed in high-income countries. The increasing incidence of malignancies in developing countries and the different characteristics among populations underscore the need for high-quality data collection and implementation of registries in these countries. Tangka *et al.* reported a wide variation in data registration in different countries, ranging from nearly 100% in North American countries to less than 10% in Asia and Central and South Americas, and only 2% in Africa.<sup>38</sup> These are only but a few examples of the existing ignorance vis-à-vis cancer that should be addressed by a target-oriented and continuous research programme. One of the principal purposes of a COU in a developing country should be promoting research in order to produce agents of new drug classes that have not yet been introduced to their market but have been successful in other regions. Furthermore, trials should be designed in order to evaluate the cardiovascular effects of developed cancer treatment agents in these countries.

It has been postulated that individual responses based on genetic and environmental variations are responsible for provoking myocardial dysfunction or causing cardio-protective effects among patients receiving cancer therapy. Different genetic SNP types have been recognized as being involved in the carrying, metabolism, and cytotoxic features of anti-cancer drugs and therapies.<sup>39–41</sup> There is a dearth of data in the existing literature on this subject; nevertheless, further evaluations and recognition of the diverse patterns in multi-ethnicity trials are required so as to address cardio-oncology concerns in different regions.

A large and dedicated team boasting expertise ranging from basic science to different medical disciplines is needed to tackle the challenges mentioned throughout this article. With respect to education, the shortage of specialists and healthcare personnel in the cardio-oncology field, given that

it is a nascent scientific endeavour, is far more noticeable in developing countries than in the developed world. We have recently launched an educational programme to train specialists with the ultimate goal of establishing a number of cardio-oncology centres nationwide. Undoubtedly, we are acutely aware of the daunting challenges ahead, financially and chronologically, in providing the required infrastructure and training sufficient trained personnel.

## Conflict of interest

The authors Azin Alizadehasl, Ahmad Amin, Majid Maleki, Feridoun Noohi, Ardeshtir Ghavamzadeh, and Melody Farrashi declare that they have no conflict of interest.

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